DISEASES OF THE PANCREAS, SERIES #7
COMPLICATIONS OF ACUTE PANCREATITIS
by Xuong Lu, Elie Aoun

INFLAMMATORY BOWEL DISEASE: A PRACTICAL APPROACH, SERIES #78
HPV INFECTION AND VACCINATION IN PATIENTS WITH INFLAMMATORY BOWEL DISEASE
by Jill K. J. Gaidos, Stephen J. Bickston

NUTRITION ISSUES IN GASTROENTEROLOGY, SERIES #110
BILE ACIDS: AN UNDERRECOGNIZED AND UNDERAPPRECIATED CAUSE OF CHRONIC DIARRHEA
by Rafiul Sameer Islam, John K. DiBaise

A CASE REPORT
HEPATOTOXICITY ASSOCIATED WITH THE USE OF WHITE FLOOD, A NUTRITIONAL SUPPLEMENT
by Stanley Martin Cohen, Elizabeth Heywood, Anjana Pillai, Joseph Ahn
PRACTICAL GASTROENTEROLOGY

Vol. XXXVI No. 10

October 2012

PRACTICAL GASTROENTEROLOGY

Publisher
Vivian M. Mahl
E-mail: practicalgastro1@aol.com

Circulation Manager: James D. Green
E-mail: practicalgastro2@aol.com

Editor: Adrien A. Mahl
E-mail: practicalgastro@aol.com

Art Director: Adrien A. Mahl

National Accounts Representative
Practical Gastroenterology
99B Main Street, Westhampton Beach, NY 11978
Telephone: (631) 288-4404
Web site: www.practicalgastro.com

Practical Gastroenterology is a professional clinical journal focusing on the diagnosis and management of digestive diseases. Each issue consists of articles on topics that physicians encounter in daily practice. Authors are selected for their expert knowledge of their topics and their participation does not imply endorsement of products advertised. Authors’ opinions expressed in their articles are not necessarily those of Practical Gastroenterology, its publisher, Editorial Board, or its advertisers. Practical Gastroenterology, its publisher, editors, Editorial Board, and its advertisers assume no liability or responsibility for any claims, actions or damages resulting from the publication of any article.

AUTHOR INFORMATION: A “Guideline for Authors” is available without charge. For a free copy, e-mail: practicalgastro@aol.com


Contents of Practical Gastroenterology are protected by the U.S. Copyright Law. Reproduction, photocopying, storage or transmission by magnetic or electronic means is strictly prohibited by law. For permission to reuse material from Practical Gastroenterology (ISSN 0277-4208), please access www.copyright.com or contact the Copyright Clearance Center, Inc. (CCC), 222 Rosewood Drive, Danvers, MA 01923, 978-750-8400. CCC is a not-for-profit organization that provides licenses and registration for a variety of uses. Special rates apply for multiple copies when used internally for educational purposes. Violation of copyright will result in legal action, including civil and/or criminal penalties, and suspension of service.

ANNUAL SUBSCRIPTION RATES. USA: 1 year $145 US, 2 years $270 US, 3 years $405 US. FOREIGN: 1 year $190 US, 2 years $340 US, 3 years $510 US. Subscription should be mailed to Practical Gastroenterology, 99B Main Street, Westhampton Beach, New York 11978.

CHANGE OF ADDRESS: Practical Gastroenterology uses the frequently updated rosters maintained by two national medical associations to mail issues of the journal to physicians who qualify. If you have been receiving Practical Gastroenterology and have had a change of professional address, please make sure to advise the appropriate association of your new address. Membership is required. For MDs, write: American Medical Association, 515 North State St., Chicago, IL 60610, (800) 662-3211; www.ama-assn.org. For DOs, write: American Osteopathic Association, 212 East Ohio St., Chicago, IL 60611, (800) 621-1773, www.osteopathic.org.

CLASSIFIED ADS: For more information on Classified Ads, contact: Practical Gastroenterology Classified Department, 99B Main Street, Westhampton Beach, New York 11978. Phone (631) 288-4404; Fax (631) 288-4435.

EDITORIAL BOARD

Rad M. Agrawal, M.D.      Denis M. McCarthy, M.D.
Theodore Bayless, M.D.    George W. Meyer, M.D.
Henry J. Binder, M.D.      Sam A. Nixon, M.D.
H. Worth Boyce, Jr., M.D.  Kevin W. Olden, M.D.
R. Keith Campbell, R.Ph.   Melissa Palmer, M.D.
William D. Carey, M.D.     C.S. Pitchumoni, M.D.
Donald O. Castell, M.D.    John F. Pohl, M.D.
Richard K. Chessler, M.D.  Carol Rees Parrish, M.S., R.D.
Murray H. Cohen, D.O.      Andrew K. Roorda, M.D.
T.S. Dharmarajan, M.D.
Anthony DiMarino, M.D.
George E. Dukes, Pharm.D.
Dayna Early, M.D.
Gerald Friedman, M.D.
Justin T. Kupec, M.D.
John M. Levey, M.D.
Richard W. McCallum, M.D.

SERIES EDITORS

Rad M. Agrawal, M.D.      Diseases of the Biliary Tract
D.O. Castell, M.D.        Diseases of the Pancreas
T.S. Dharmarajan, M.D.    GERD in the 21st Century
C.S. Pitchumoni, M.D.    Geriatric Gastroenterology
Jack A. Di Palma, M.D.    Foodborne Illness
Dayna Early, M.D.         Sex-Based Differences in Gastroenterology
Jorge L. Herrera, M.D.    Viral Hepatitis
Muralidhar Jatla, M.D.    Celiac Disease: A Comprehensive
Ritu Verma, M.D.           Review and Update
Seymour Katz, M.D.        Inflammatory Bowel Disease: A Practical Approach
Justin T. Kupec, M.D.
Kevin W. Olden, M.D.
Melissa Palmer, M.D.
Henry P. Parkman, M.D.
Andrew K. Roorda, M.D.
Melvin Schapiro, M.D.

DEPARTMENT EDITORS

Murray H. Cohen, D.O.      From the Literature
C.S. Pitchumoni, M.D.      Fellows’ Corner
Rad M. Agrawal, M.D.       Book Reviews
John F. Pohl, M.D.         From the Pediatric Literature
                          Practical Endoscopy
                          Pearls of Gastroenterology

Christina M. Surawicz, M.D.
Complications Of Acute Pancreatitis
by Xuong Lu, Elie Aoun

Acute pancreatitis is an aggressive inflammatory process which may have variable regional and remote organ involvement. The onset of complications may occur at any time during the course of the acute illness. This review focuses on the local complications of acute pancreatitis and their management thereof.

HPV Infection and Vaccination in Patients with Inflammatory Bowel Disease
by Jill K. J. Gaidos, Stephen J. Bickston

Human papillomavirus (HPV) is an extremely prevalent infection, which can lead to genital warts or anogenital cancers. Studies have shown an increased prevalence of cervical dysplasia, a precursor to cervical cancer, among women with inflammatory bowel disease (IBD), particularly among women on immunosuppressive medications. Here we discuss vaccination for HPV which is approved and recommended for use in all individuals ages 9 - 26, including immunosuppressed patients.

Bile Acids: An Underrecognized and Underappreciated Cause of Chronic Diarrhea
by Rafiul Sameer Islam, John K. DiBaise

Bile acid malabsorption (BAM) remains an underrecognized cause of chronic diarrhea and results in many patients receiving an incorrect diagnosis, thereby delaying proper treatment. The goal of this review is to raise awareness of this clinical condition so that it may be considered in the differential diagnosis of chronic diarrhea.

Hepatotoxicity Associated with the Use of White Flood, a Nutritional Supplement
by Stanley Martin Cohen, Elizabeth Heywood, Anjana Pillai, Joseph Ahn
DEPARTMENTS

Crossword Puzzle 58
by Myles Mellor

From the Pediatric Gastroenterology Literature 50
by John F. Pohl, M.D., editor of “From the Pediatric Gastroenterology Literature” is on the Editorial Board of Practical Gastroenterology.

Medical Bulletin Board 51
News items of interest to the nation’s gastroenterologists.

Meetings Calendar 57
Meetings, events, courses, symposia, and their contacts.

Reader Request Fax Form 56
Readers may obtain additional information about products and services that appear in Practical Gastroenterology.
Complications of Acute Pancreatitis

INTRODUCTION

Acute pancreatitis is an acute inflammatory process of the pancreas, which has variable involvement of other regional tissues and/or remote organ systems. The disease can be classified as mild or severe depending on the extent of inflammation and organ involvement. Mild pancreatitis consists of interstitial (edematous) pancreatitis on imaging with minimal or no extrapancreatic organ dysfunction or involvement. Severe pancreatitis manifests with organ failure in addition to local complications such as pseudocysts, necrosis, abscess formation, fistulization, or vascular complications. This review focuses on the local complications of acute pancreatitis and their management thereof.

Pseudocysts

Pseudocysts can develop after an episode of acute pancreatitis in approximately 10% of cases. A pancreatic pseudocyst is a maturing circumscribed collection of pancreatic secretions encased in granulation tissue occurring in or around the pancreas as a result of inflammatory pancreatitis with or without ductal disruption (Figure 1). Pseudocysts account for about 80% of cystic lesions of the pancreas. They may be single or multiple, within or outside of the pancreas, and can vary in size. Most pseudocysts communicate with the pancreatic ductal system and contain high concentrations of digestive enzymes. The walls of a pseudocyst are formed by the adjacent structures, which may include the stomach, transverse mesocolon, gastrocolic omentum, and the pancreas itself. The key feature of a pseudocyst is the lining, which contains fibrous material and granulation tissue and has no true epithelial lining. This distinguishes pseudocysts from a true cystic lesion of the pancreas.

There have been two suggested hypotheses for pseudocyst formation as a result of acute pancreatitis. The first is that pancreatic inflammation may result in necrosis of pancreatic and peripancreatic tissue, which can then progress into liquefaction of the parenchyma and surrounding tissue with subsequent organization and eventual evolvement into a pseudocyst. The second hypothesis suggests that pancreatic parenchymal necrosis leads to ductal disruption and gross leakage of pancreatic fluid, which subsequently undergoes organization and evolvement into a pseudocyst.

The classification of these pancreatic fluid collections as pseudocysts versus pancreatic necrosis, pancreatic abscesses, or peripancreatic fluid collections can be difficult. The nomenclature of pancreatic pseudocyst was agreed upon by a consensus of experts at the Atlanta Symposium who defined a pseudocyst as a fluid collection that was >4 weeks old and surrounded by a well-defined wall; however, in clinical practice,
Complications of Acute Pancreatitis

DISEASES OF THE PANCREAS, SERIES #7

fluid collections found on imaging during and after an episode of acute pancreatitis may not be so easily classified.\(^1,6\) If the diagnosis is questionable, further testing may be performed including aspiration of fluid under computed tomography (CT) or endoscopic ultrasound (EUS) guidance. Compared to the other types of acute pancreatic fluid collections, pancreatic pseudocysts tend to have higher concentrations of pancreatic enzymes and minimal to no tissue debris and are for the most part sterile.\(^6\) The diagnosis of pseudocyst may also be supported by the presence of pancreatic ascites or pancreatic pleural effusion that have high amylase concentrations >1000 IU/L.\(^7\)

**Management**

The traditional treatment of pseudocysts was based on a classic study that suggested that a pseudocyst persisting for >6 weeks rarely resolved and had a complication rate nearing 50% during continued observation.\(^10\) However, this study was comprised primarily of inner-city alcoholics who had a high incidence of acute alcoholic pancreatitis, and as such, these observations may not apply to other populations. In fact, recent data suggest that an asymptomatic pseudocyst does not require treatment regardless of size.\(^8,9\) A retrospective review of 68 patients with a pseudocyst followed conservatively showed that there was only a 9% incidence of major complications including perforation, pseudoaneurysm, and abscess formation. Twenty-seven percent of patients underwent elective surgery due mostly to pseudocyst enlargement with associated pain. Sixty-three percent of patients remained well without symptoms or complications for a mean of 51 months.\(^8\) These findings suggest that it may be satisfactory to monitor asymptomatic pseudocysts with serial imaging.

The most commonly reported symptom of a pseudocyst is upper abdominal pain, but other less common symptoms include early satiety, nausea, vomiting, jaundice, pruritus, edema, or gastrointestinal bleeding. These symptoms correlate to local obstruction of structures such as the gastric outlet, IVC, common bile duct, small bowel, colon, splenic, or portal veins and are usually related to the pseudocyst size and its location. Occasionally, a pseudocyst can rupture into the stomach in the small bowel (Figure 2). Other reported complications attributed to pseudocysts include infection, intracystic hemorrhage, or rupture, leading to pancreatic ascites. Pseudocysts have also been reported to migrate into chest as well as other unusual locations.\(^9\)

In the clinical setting of a pseudocyst related to acute pancreatitis, new symptoms of abdominal pain, fever, or chills should be recognized as possible emergence of an infection or abscess formation, and appropriate surgical, endoscopic, or radiologic management should be undertaken depending on the presenting symptoms and findings.

**Drainage**

Surgical drainage was at one time the only form of therapy available for symptomatic pseudocysts or pseudocysts that required drainage due to infection. However, over the last 10 years, imaging-guided percutaneous catheter drainage and endoscopic drainage have become increasingly popular. However, to date, there are no randomized, comparative studies that evaluate the efficacy or morbidity associated with these drainage modalities. Local expertise has driven the use of one method over another in determining which approach is most appropriate.\(^8,9,11,12\)

Surgical drainage remains the most accepted modality for pancreatic pseudocyst management. The surgical literature describes newer laparoscopic methods for drainage, though most data have come from open surgical drainage procedures. Open surgical drainage may be accomplished via cystgastrostomy, cystenterostomy (with or without creation of a Roux Limb), or surgical resection. First described in 1994, several different approaches of laparoscopic drainage have been used. Laparoscopic cystgastrostomy can be performed using an anterior transgastric approach requiring an anterior gastrostomy for access with cystgastrostomy creation via the posterior gastric wall.\(^13,14\) A posterior approach has also been described with creation of a single gastrostomy in continuity with the pseudocyst via the lesser sac.\(^15\) The latter is considered technically easier and is associated with less intraoperative bleeding.\(^14,16,17\)

In general, morbidity and mortality associated with surgical drainage has been shown to be substantial with rates of 25% and 5%, respectively.\(^18-20\) Some series have reported pseudocyst recurrence rates after surgical drainage to be as high 15%, and can be more frequent if the main pancreatic duct is obstructed downstream from the surgical anastomosis.\(^20\) Preoperative endoscopic retrograde cholangiopancreatography (ERCP) is usually performed to determine if ductal obstruction exists, and

(continued on page 14)
Complications of Acute Pancreatitis

DISEASES OF THE PANCREAS, SERIES #7

(continued from page 12)
in such cases, pseudocyst resections can be offered.

Imaging-guided percutaneous catheter drainage has been reported to be as effective as surgical management of a pseudocyst whether the cyst is sterile or infected. However, there are several complications associated with this procedure, with the most common being drain-track infections, occurring in up to 50% of cases. The more concerning complication, however, is the formation of an external fistula. This risk is associated with any percutaneous catheter intervention, but in the setting of pseudocyst drainage with high concentration of pancreatic enzymes, it is much higher. Ductal anatomy has been shown to correlate with both the success of percutaneous method as well as the development of complications after percutaneous drainage. Pseudocysts with normal pancreatic ducts and those associated with pancreatic duct strictures without duct disruption or cyst communication have higher rates of successful drainage. Strictures in association with pancreatic duct disruption and cyst communication and those associated with complete cut-off of the pancreatic duct have relatively poor outcomes. The latter features also predispose to long-term pancreatic external fistula formation. ERCP is usually performed to determine ductal anatomy prior to percutaneous drainage. Ill-defined anatomy is considered to be a relative contraindication to imaging-guided percutaneous drainage.

Pseudocyst decompression can be achieved by two endoscopic methods. Transpapillarai drainage via stenting through the ampulla directly into the pseudocyst itself or by creating an endoscopically placed cystgastrostomy or cystduodenostomy. Studies have not shown a significant difference in outcomes for the respective approaches in pseudocyst drainage. Regardless of the technique used, the catheter is removed after three to four weeks if closure of the pseudocyst is seen on imaging.

Long-term resolution with successful endoscopic drainage of pseudocysts has been reported in most series, with rates ranging from 65% to 89%. The major complication with endoscopic pseudocyst drainage is bleeding, retroperitoneal perforation, and infection. Bleeding has been considered to be the most important, with about a 5% risk of requiring surgical interventions. Some series have suggested that nasocystic drainage

Figure 1. Pancreatic pseudocyst
with irrigation may prevent occlusion and can be used in infected pseudocysts or possibly even in organized necrosis.\textsuperscript{28,29} Recurrence rates have been reported to range from 6\% to 18\%; however, rates may be reduced with long-term pancreatic duct stenting in patients with severe duct disruption.\textsuperscript{30}

**Necrotizing Pancreatitis and Abscess Formation**

Pancreatic necrosis is a local complication that can occur in up to 10\%-20\% of patients suffering from acute pancreatitis.\textsuperscript{31} The diagnosis can be made based on imaging and is defined by the presence of $>$30\% of nonenhancement of the pancreas on contrast-enhanced CT or magnetic resonance imaging (MRI). Infected necrosis refers to bacterial contamination of necrotic pancreatic tissue in the absence of abscess formation. It can progress to abscess formation and is defined as a collection of pus resulting from infected liquefaction of necrotic pancreatic tissue. Infected pseudocysts, as described previously, are an infected fluid collection with high concentrations of pancreatic enzymes within a defined fibrous wall lacking underlying epithelial lining. Although there is overlap in the characterization of localized infections of the pancreas, recognizing the nomenclature describing the complication has importance with regards to management. Figure 3 shows evidence of walled off pancreatic necrosis on CT scan.

**Sterile Necrosis**

Sterile pancreatic necrosis occurs early in the course of pancreatitis and is typically seen within the first 10–14 days of illness. Contrast-enhanced CT is the gold standard in the diagnosis of necrotizing pancreatitis. The development of necrosis is a continuous process that occurs within hours of symptom onset; however, contrast-enhanced CT in the first several days will miss the formation of necrotic parenchyma and can be misleading. The sensitivity of contrast-enhanced CT for pancreatic necrosis nears 100\% between 4 to 10 days after onset of pancreatitis.\textsuperscript{32} Often patients with necrosis present as necrotizing pancreatitis. This is the most severe presentation of pancreatic inflammation. The amount of necrotic tissue is the strongest predictor of mortality in necrotizing pancreatitis.

![Figure 2. (A) Pseudocyst rupturing into the duodenum seen on upper endoscopy. (B) Visualization of the cyst cavity endoscopically.](image-url)
After diagnosis, the treatment is maximal supportive care including nutrition and preventing infections from intravenous lines. The role for prophylactic antibiotics to prevent infection has been shown to be questionable and not recommended. Surgical debridement of sterile pancreatic necrosis has not proven to improve morbidity or mortality in majority of patients. However, surgical debridement is often needed when necrosis becomes infected.

**Infected Necrosis**

Infected pancreatic necrosis generally occurs after 10–14 days of illness. Bacterial infection is a major determinant of mortality. Severe systemic complications are common in patients with sterile necrosis, but mortality rates are relatively low, with a reported incidence of 5%–10%. With development of pancreatic infection, the mortality increases to 20%–30%, despite surgical debridement. Diagnosis of infection can be made via fine-needle aspiration (FNA). CT-guided FNA has been safe in the diagnosis of infected necrosis. The gram stain alone has a sensitivity of almost 95%. In the event of a negative FNA with a persistent suspicion for infection, repeat aspirations can be performed every 4 to 7 days.

In patients diagnosed with infected necrosis who have persistent sepsis or organ failure, surgical debridement should be strongly considered. However, in stable patients with infected necrosis, maximal supportive care and the use of antibiotics should be provided. Optimal timing for surgical debridement is at least 3 to 4 weeks after onset of illness. Delayed debridement allows for clinical stabilization of the patient, resolution of organ dysfunction, lowered inflammatory reaction in the retroperitoneum, and the delineation of live and dead tissue via organization and formation of a fibrous wall. This clinical entity is known as walled-off pancreatic necrosis (WOPN). The benefits of waiting for WOPN is the resolution of systemic inflammation and determination of live and dead tissue delineation which would result in less invasive methods of debridement. Early-phase debridement within the first 3 to 4 weeks requires an open surgical approach where as late-phase debridement of WOPN can be treated laparoscopically, percutaneously, or endoscopically.

**Pancreatic Abscess**

Pancreatic abscess is a late complication of acute necrotizing pancreatitis, which occurs more than 4 weeks after the initial illness. The management and complications are similar to that of infected pseudocysts. Abscess formation can cause pressure effects and obstruction by compression of surrounding structures, including the colon, stomach, duodenum, and the common bile duct. The mortality rate associated with pancreatic abscess is generally much lower than that of infected necrosis. Initiation of antibiotics followed by surgical, percutaneous, or endoscopic drainage should be performed. Abscesses that are drained percutaneously or endoscopically which do not show clinical improvement should undergo surgical drainage immediately.

Surgical debridement or drainage of the pancreas is the mainstay of treatment for infected pancreatic necrosis or abscesses. Percutaneous drainage is primarily a bridging technique for patients that are not stable enough to undergo surgical debridement, although about 35% of patients can be managed with percutaneous drainage alone. Percutaneous drainage compared with open pancreatic debridement in select cases has shown decreased new onset multi-system organ failure, incisional hernias, and interval development of diabetes. This had no significant effect on mortality. In general, CT guidance is used to establish percutaneous access into the pancreatic fluid collections using a transperitoneal route if available to avoid solid organs, intervening bowel, or vasculature. The limitations to this approach are due to location of the space that requires drainage, catheter diameter, viscosity of the fluid, and the amount of debris present. Due to these limitations, the drainage catheter generally requires meticulous maintenance as well as frequent replacement.

Endoscopic debridement for infected necrosis has been described via a transgastric approach but is limited to patients who are stable and have developed WOPN. The overall approach is similar to that of pseudocyst drainage. Once a cystgastrostomy has been established, direct endoscopic debridement can be performed using a forward viewing endoscope. Following mechanical debridement, double pigtail stents are placed in the cavity, and some experts suggest placing a nasocystic tube along side the stents for post procedure irrigation. Serial imaging can be used at 2-week intervals until resolution of necrosis is achieved. Similar to percutaneous drainage, data suggest that 33% of patients treated with endoscopic debridement will eventually need open surgical debridement.
Vascular Complications

The incidence of vascular complications related to acute pancreatitis is not known, though it has been speculated to have an incidence nearing 25% in acute pancreatitis cases.39 The most common complications are pseudocyst hemorrhage, erosions of the gastrointestinal vessels, venous thrombosis, variceal formation, and pseudoaneurysm formation. The pathogenesis of vascular complications is multifactorial, but the predominant mediators are local spread of inflammation, irritative effects of activated pancreatic enzymes, and pressure necrosis due to fluid collection or inflammatory debris on surrounding structures. The mortality related with hemorrhage associated with these complications of acute pancreatitis has been reported to occur in up to 14.5% of the time, and there does appear to be a correlation with severity of underlying illness.40-42

Pseudoaneurysm

A pseudoaneurysm is a collection of blood and blood clot that has formed outside of a vessel. Pseudoaneurysms have been reported to occur in 3.5%–10% of patients with pancreatitis.43 Arteries most commonly involved are the splenic, gastroduodenal, and pancreaticoduodenal. These vessels are involved in approximately 90% of all pseudoaneurysms related to acute pancreatitis.44,45 Rupture of pseudoaneurysms is a serious complication of pancreatitis and have been know to bleed into the pseudocyst, the gastrointestinal tract, peritoneal cavity or pancreatic parenchyma.46 The diagnosis is not always clear as the patient may have hemodynamic instability or multiple organ dysfunction related to severe pancreatitis. The patient may present with abdominal pain, signs of exsanguinating blood loss, or slow intermittent bleeding. A sudden exsanguinating process, which leads to death within minutes to hours, has been reported in 7.5% of patients with pseudoaneurysm ruptures.47

Regardless of size, non-bleeding pseudoaneurysms do not require treatment and are usually observed and diagnosed based on dynamic contrast-enhanced CT scan. The gold standard for diagnosis and preferred method of treatment of ruptured pseudoaneurysms in stable patients is angiography. Angioembolization has been used extensively in the treatment of visceral artery pseudoaneurysms and is considered much less invasive than surgical options. The advent of newer catheters, embolic material, and improvement in technical expertise has been demonstrated with increasing success over the past decade (as high as 67%–100%).48

Percutaneous ultrasound guided thrombin injections have also been used successfully in treatment of pseudoaneurysms.49 This technique has been described as first-line management or as adjuvant treatment with arterioembolization. However, to date, there are no large, prospective studies that compare the efficacy of thrombin injection to arterioembolization in pancreatic pseudoaneurysms.

Surgical management of pseudoaneurysms has been limited to patients with hemodynamic instability and/or failure of radiologic techniques. The most common surgical procedure is suture ligation of the bleeding point; however, recurrence of bleeding has been reported to be high. Due to excellent collateral circulation of the pancreas and peri-pancreatic structures, it is optimal to ligate the artery proximal and distal to the pseudoaneurysm. Primary resection of the pseudoaneurysm with or without pancreatic resection may be required if ligation of the proximal and distal ends of the bleeding vessel are not achieved.50,51

Venous Thrombosis

Venous thrombosis may be observed in acute pancreatitis and is related to acute inflammatory processes of the pancreas adjacent to venous structures. Isolated splenic vein thrombosis is the most common type, and, in some case series, has had a reported incidence as high as 42% in acute pancreatitis cases.52 Less commonly, portal and superior mesenteric vein thrombosis can occur as a results of pancreatitis. The pathogenesis is related to intimal injury and compression as a result of the close proximity of the venous vasculature to the pancreas, most specifically the splenic vein. Stasis of blood flow occurs from these intrinsic and extrinsic factors and eventually leads to thrombosis. Development of venous stasis has been hypothesized to occur as a result of compression by pseudocyst and/or enlarged edematous pancreatic parenchyma. Splenic vein obstruction can be seen of the pseudocyst tail in nearly 30% of cases.53

Splenic vein thrombosis (SVT) may be silent or present as gastrointestinal bleeding (anemia, hematemesis, melena, or hematochezia). Occasionally thrombocytopenia, pancytopenia, and/or abdominal pain can occur due to splenomegaly.54 SVT is asymptomatic in the majority of cases and may present as an incidental finding on CT scan. Dynamic-enhanced CT scan can be done with a sensitivity of 71% in detecting SVT.
Venography is the gold standard for diagnosing SVT. Many patients with SVT develop silent collaterals without gastric or esophageal varices and are extremely unlikely to bleed.

Management of SVT should be focused on observation due to the possibility of variceal formation and subsequent risk of upper gastrointestinal hemorrhage in the future. However, data suggest that variceal formation is unlikely if they were not present at the time of diagnosis. At this time, there are no guidelines for the routine surveillance of interval variceal development. Patients who develop bleeding related to gastric or esophageal varices can be temporized endoscopically with variceal band ligation. Splenectomy is curative, and the treatment of choice in symptomatic patients that are surgical candidates. In patients that are at high surgical risk or have technically difficult to excise spleens, radiographic arterioembolization may be a possible alternative or bridge to surgery. The role of splenectomy in asymptomatic SVT associated with gastric varices remains controversial. Long-term observations show that bleeding risk in patients with SVT over time exceeds the risk of elective splenectomy due to post splenectomy sepsis; thus, prophylactic splenectomy may be useful. Opposing expert opinion suggests that observation followed by splenectomy after the first episode of variceal bleeding may be a reasonable approach, as bleeding appears to be uncommon with a reported incidence of only 4% in asymptomatic patients with gastric varices in association with SVT. However, there is no definitive way to accurately predict the risk of variceal hemorrhage, and thus, the possibility of life-threatening bleeding cannot be excluded with certainty. Bleeding risk is greater in patients with larger varices or when red wale markings are observed during endoscopy, which may be beneficial in decision making. Patients with hypersplenism presenting as pain or cytopenias may also have a greater justification for undergoing prophylactic splenectomies to prevent bleeding.

**Other Bleeding Complications**

Other bleeding complications include postnecrosectomy bleeding, which can be a result of overly aggressive debridement and placement and/or use of noncompliant drainage tubes next to a vascular structure resulting in pressure necrosis and direct erosion into a vessel. In some cases, incomplete debridement can result in sepsis and erosion into vascular structures as well. Data
suggest that bleeding complications are significantly more common in interventions that occur in the acute phase versus after delayed interventions. Radiologic arterioembolization is the main stay of management with surgery reserved for refractory cases or for patients with hemodynamic instability. Rarely, bleeding can occur into the pancreatic duct, which is known as hemosuccus pancreaticus; however, this is more typically seen as a complication of chronic pancreatitis. Intermittent, low-grade gastrointestinal bleeding up to exsanguinating bleeding has been described as a result of hemosuccus pancreaticus. Due to rare occurrence, there are limited data on its management. Options include radiographic arterioembolization versus surgical vessel suture ligation with or without distal pancreatectomy. Mortality rates associated with surgery have been reported as high as 20%–25%, though re-bleeding rates are significantly lower than that of arterioembolization.

Other Complications of Pancreatitis

Isolated splenic complications of acute pancreatitis are uncommon. Intrasplenic pseudocysts, splenic infarction, necrosis, rupture, and hematoma have all been reported as possible complications. Some of these complications can be life threatening and require emergent splenectomy, and if necessary, distal pancreatectomy as definitive treatment.

Bowel compression has been reported as a result of pressure necrosis from inflammatory debris from the tail of the pancreas. This may result in signs and symptoms of partial or complete obstruction and may even result in fistulization of the small or large bowel. The left colon is the most common site of compression and fistulization. Decompression of the obstructing lesion can be done percutaneously, endoscopically, or surgically depending on the type of lesion. After fistulization has occurred, treatment is limited to surgical repair or resection.

Common bile duct obstruction may be a complication of acute pancreatitis. This is normally seen in the early symptomatic phase of illness and is related to the inflammatory mass in the head of the pancreas, pseudocyst, or fluid collections. Typically, the distal common bile duct is affected and subsides with clinical improvement of underlying illness. In patients who develop biliary sepsis or intractable pruritus, management options include endoscopic, surgical, or percutaneous decompression. Endoscopic or percutaneous decompression is associated with lower morbidity and should be considered first-line therapy. Patients generally need short-term decompression with stents or catheters as resolution is almost always seen once clinical improvement of the underlying illness occurs.

CONCLUSION

In conclusion, acute pancreatitis is an aggressive inflammatory process which may have variable regional and remote organ involvement. Local complications of pancreatitis are many and may result in varying degree of morbidity and or mortality. The onset of complications may occur at any time during the course of the acute illness. Careful monitoring of patients taken to rapidly recognize complications can ultimately change the course of disease. Management of complications is dictated by the identification and understanding of specific complications and also on the knowledge and availability of local expertise.

References

Complications of Acute Pancreatitis

DISEASES OF THE PANCREAS, SERIES #7

(continued from page 21)

HPV Infection and Vaccination in Patients with Inflammatory Bowel Disease

Human papillomavirus (HPV) is the most common sexually transmitted infection in the United States and can lead to genital warts and anogenital cancers, with the highest prevalence in cervical and anal cancers. Studies have shown an increased prevalence of cervical dysplasia, a precursor to cervical cancer, among women with inflammatory bowel disease (IBD), particularly among women on immunosuppressive medications. Vaccination for HPV has been available since 2006 and is recommended for all individuals ages 11 - 26, including those with IBD. The vaccine is safe for use in immunosuppressed patients. Research has shown that immunosuppressed patients mount an adequate immune response following vaccination for HPV. Screening for cervical dysplasia should continue at regular intervals as the HPV vaccine does not cover all high-risk HPV types and Pap testing is still needed to detect cervical dysplasia. There are currently no screening guidelines for anal cancer.

BACKGROUND

Human papillomavirus (HPV) is the most common sexually transmitted infection in the United States with over 6 million new cases each year. There are over 100 types of HPV, over 40 of which are spread through skin-to-skin contact during intercourse and can lead to anogenital infections. Over half of all sexually active individuals will be infected with at least one HPV type during their lifetime. The sexually transmitted types are subdivided into high-risk or low-risk groups based on their oncogenicity. Infection with a low-risk HPV type, such as type 6 or 11, can result in cervical dysplasia or genital warts. Infection with a high-risk type, such as type 16 or 18, increases the risk for developing cancers, particularly cervical and anal cancers. A high-risk HPV type is detected in almost all cases of cervical cancer, with over 70% of all worldwide cases of cervical cancers due to types 16 and 18. High-risk HPV types also are responsible for approximately 90% of all anal cancers. As well, these high-risk HPV types can lead to other cancers such as oropharyngeal, vulvar, vaginal, and penile cancers.
Despite the increased risk for cancer, most infections with HPV in immune competent individuals are transient and asymptomatic. Almost three quarters of new HPV infections will resolve within 1 year while approximately 90% will resolve within 2 years. Persistent infection with a high-risk HPV type, particularly type 16, is the most important predictor for developing cervical dysplasia or cancer. Immune suppression is another risk factor that plays a key role in the progression of an HPV infection to cervical cancer. Studies in human immunodeficiency virus (HIV) populations and in women who have undergone organ transplantation confirm an increased incidence of cervical dysplasia among these populations.

Because of the prevalence of these infections and the risk of progression to cancer, two vaccines have been developed to help protect patients from HPV. One is a quadrivalent HPV vaccine, which covers HPV types 6, 11, 16 and 18 (HPV4; Gardasil, Merck) while the other is a bivalent HPV vaccine, which covers only HPV types 16 and 18 (HPV2; Cervarix, GlaxoSmithKline). The HPV4 vaccine has been approved by the Food and Drug Administration for use in females and males ages 9 – 26 and the HPV2 vaccine has been approved for use in females ages 9 – 25. The Advisory Committee on Immunization Practices recommends HPV vaccination for all children beginning at age 11 up to 26 years of age.7,8

HPV in Inflammatory Bowel Disease

Inflammatory bowel disease (IBD) refers to a group of chronic inflammatory diseases, including Crohn’s disease and ulcerative colitis. These conditions involve inflammation throughout the GI tract and frequently require treatment with immunosuppressive medications. A handful of studies have examined the prevalence of cervical dysplasia, resulting from persistent HPV infection, among women with IBD (Table 1.9-13). The results of the studies are mixed, with some showing IBD brings an independently increased risk of cervical dysplasia, others showing an increased risk associated with medications for IBD, while others found no increased risk. Due to limitations in study design, only one of these prior studies was able to assess for the presence of HPV infection. Kane et al. found an increased incidence of cervical abnormalities in women with IBD and more advanced lesions in those being treated with immunosuppressive therapies. All abnormal Pap results tested positive for HPV types 16 or 18.12 Fewer studies have examined the risk for anal cancer among the IBD population. A population-based case-control study out of Denmark and Sweden evaluated the risk for HPV positive and HPV negative anal carcinoma among subjects diagnosed with anal cancer, rectal cancer and population controls.16 Subjects with IBD made up < 1% of the study population. Despite the lack of power in the analysis, the researchers determined that ulcerative colitis and Crohn’s disease were not associated with an increased risk for anal cancer.

HPV Vaccination Recommendations in Inflammatory Bowel Disease

Over the past several years, there has been an influx of publications reviewing indications for vaccination among patients with IBD. Vaccinations are of particular importance among this population as a large percentage of these patients are currently taking or will be taking immunosuppressive medications to treat their disease, which increases their risk for acquiring certain infections. All vaccination guidelines published since the HPV vaccine has become available have recommended its use for this population.

HPV preferentially infects the epithelial cells and causes inactive cells to actively replicate, resulting in dysplasia. Because these infections are limited to the epithelium, the virus is somewhat shielded from a host immune response. This can lead to persistent infections and also limits the use of antibody testing to assess for previous or current infection. A study of antibody response to incident infection found only 54 - 69% of women with HPV 16, 6, or 18 infection had positive antibodies.17 Current testing requires the presence of HPV DNA or RNA, on cervical smear, to detect an HPV infection. In some cases there is no way to definitively determine prior exposure.

Given the lack of sensitivity of antibody testing to detect prior exposure, HPV vaccination is recommended for all individuals ages 9 - 26, regardless of sexual history or history of cervical dysplasia, as the likelihood of exposure to all HPV types covered by the vaccine is low. In addition, the antigen in the HPV vaccine is a viral L1 capsid protein and is non-infectious. It is safe to give to patients who are already immune suppressed, however it is not recommended during pregnancy.

When vaccinating immunosuppressed individuals, there is some question as to whether they will develop an adequate immunologic response. One study examined
the immunologic response of 30 female IBD patients on immunosuppressive medications who received the quadrivalent HPV vaccine. They found that over 90% of the subjects became seropositive to all of the 4 HPV types, with their response comparable to a historical control group. Even with an adequate immune response, HPV vaccines do not include all high-risk types and vaccination does not eliminate the need for regular screening.

Table 1. Cervical Dysplasia in Women with IBD

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Patient Population</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bhatia, 2006</td>
<td>116 with IBD (64 CD, 52 UC), 116 age-matched controls</td>
<td>Abnormal Paps in 18% with IBD vs 5% of controls (p=0.004)</td>
</tr>
<tr>
<td>Venkatesan, 2006</td>
<td>518 with IBD</td>
<td>Abnormal Pap in 25/518 (4.8%). Infliximab use associated with OR 5.0 (2.11 – 11.85, p=0.0001)</td>
</tr>
<tr>
<td>Hutfless, 2008</td>
<td>1165 with IBD (427 CD, 738 UC), 12124 age-matched controls</td>
<td>10 (0.85%) cervical cancers (3CD, 7 UC) among IBD, 72 (0.59%) cancers among controls. Adjusted OR for cervical cancer in IBD 1.45 (0.74 – 3.84)</td>
</tr>
<tr>
<td>Kane, 2008</td>
<td>40 with IBD (32 CD, 8 UC) with 134 Paps; age-, race-, and parity-matched controls</td>
<td>42.5% abnormal Paps in IBD vs 7% in controls; higher grade lesions in IBD (p&lt;0.001); exposure to IS more likely to have cervical dysplasia (p&lt;0.001); &gt; 6 months exposures OR 1.5 (1.2 – 4.1; p=0.02)</td>
</tr>
<tr>
<td>Lees, 2009</td>
<td>411 with IBD (204 CD, 107 UC), 1644 controls from same geographic location</td>
<td>No difference in rates of cervical dysplasia; more abnormal Paps among smokers with IBD vs non-smokers and never smokers with IBD 27.4% vs 11.4% (p=0.001; OR 2.95, 1.55 – 5.50)</td>
</tr>
<tr>
<td>Singh, 2008</td>
<td>525 with IBD (292 CD, 233 UC); 19,692 with abnormal Paps matched with 57,898 controls</td>
<td>No association between abnormal Pap and UC; increased risk in CD limited to women exposed to &gt; 10 prescriptions for OCPs (OR 1.66, 1.08 – 2.54); combined exposure to steroids and IS increased risk of cervical abnormality (OR 1.41, 1.09 – 1.81)</td>
</tr>
<tr>
<td>Marehbian, 2009</td>
<td>22,310 CD; 111,550 controls</td>
<td>Monotherapy IS increased risk of cervical dysplasia (HR 1.5, 1.2 – 2.0); use of 2 – 3 IS medications further increased risk (HR 1.8, 1.1 – 3.0)</td>
</tr>
</tbody>
</table>

IBD = inflammatory bowel disease; CD = Crohn’s disease; UC = ulcerative colitis; Pap = Papanicolaou testing; IS = immunosuppressive medications, including steroids, immunomodulators, and biologic agents; OCP = oral contraceptive pills.
HPV Infection and Vaccination in Patients with IBD

INFLAMMATORY BOWEL DISEASE: A PRACTICAL APPROACH, SERIES #78

HPV Screening Recommendations

Updated recommendations for cervical cancer screening were published in March 2012 by the US Preventative Task Force. These include a later onset of screening and a decreased frequency of screening. These recommendations clearly state that they do not apply to women who are immune suppressed as they are at an increased risk for developing cervical cancer. The American College of Obstetrics and Gynecology recommends that women who are immune suppressed undergo cervical cancer screening every 6 months for the first year of immune suppression, then annually thereafter. There is no indication whether HPV testing should be performed at each screening or if cytologic exam is adequate. However, it is becoming common practice for reflex HPV testing to be performed if the cytologic exam is abnormal.

Several studies have found a lower rate of cervical cancer screening among women with IBD. Long et al. showed that women with IBD who are on immunosuppressive medications, i.e. those with the highest risk for developing dysplasia, had cervical cancer screening less frequently than their matched controls.20 Similarly, Selby et al. showed an overall lower rate of receipt of preventative care, including cervical cancer screening, among IBD patients compared to the general population.20

Anal HPV infections and anal cancer precursors are commonly diagnosed in men who have sex with men. At this time, there are no FDA-approved tests for detecting HPV infections in men or screening guidelines for detecting HPV-induced dysplasia or cancer of the anus in this population. A systematic review and meta-analysis from May 2012 determined that the rate of progression from anal HPV to cancer among men who have sex with men was too low for a screening program to be effective.21 Continued research in HPV may yield specific recommendations for men.

In summary, HPV is an extremely prevalent infection, which can lead to genital warts or anogenital cancers. The HPV vaccination is approved and recommended for use in all individuals ages 9 - 26, including immunosuppressed patients. One study in immune suppressed women with IBD has shown an adequate immune response following vaccination. Our center’s practice is to vaccinate women and men with IBD. This approach must be tempered by the fact that available HPV vaccines do NOT cover all high-risk HPV types; regular screening is still recommended.

References

Bile acid malabsorption is a common cause of chronic watery diarrhea; however, its role appears to be poorly appreciated among clinicians. As such, bile acid diarrhea remains an underrecognized cause of chronic diarrhea, resulting in many patients incorrectly diagnosed and interfering and delaying proper treatment. In this review, we briefly discuss the synthesis, enterohepatic circulation, and function of bile acids. We then focus on the role of bile acids in bile acid malabsorption including the diagnostic and treatment options. By recognizing that bile acid malabsorption is a relatively common cause of chronic diarrhea, we hope that more physicians will more effectively evaluate and treat patients with this condition.

INTRODUCTION

Diarrhea caused by bile acids was first recognized in 1967, when Alan Hofmann described this phenomenon as cholerhetic enteropathy.\(^1\) Despite more than 40 years since the initial report, bile acid diarrhea remains an underrecognized and underappreciated cause of chronic diarrhea. One recent report found that only 6% of British gastroenterologists investigate for bile acid malabsorption (BAM) as part of the first-line testing in patients with chronic diarrhea, while 61% consider the diagnosis only in selected patients or not at all.\(^2\) As a consequence, many patients are diagnosed with other causes of diarrhea or are considered to have irritable bowel syndrome or functional diarrhea by exclusion, thereby interfering with, and delaying proper treatment. The goal of this review is to raise awareness of this clinical condition so that it may be considered in the differential diagnosis of chronic diarrhea. We will first review bile acid synthesis and enterohepatic circulation, followed by a discussion of specific disorders involving BAM including their diagnosis and treatment.

Bile Acid Synthesis

Bile acids are produced in the liver as end products of cholesterol metabolism. Bile acid synthesis occurs by two pathways: the classical (neutral) pathway via
Bile Acids

(continued from page 32)

microsomal cholesterol 7α-hydroxylase (CYP7A1), or the alternative (acidic) pathway via mitochondrial sterol 27-hydroxylase (CYP27A1). The classical pathway, which is responsible for 90-95% of bile acid synthesis in humans, begins with 7α-hydroxylation of cholesterol catalyzed by CYP7A1, the rate-limiting step (Figure 1). This pathway occurs exclusively in the liver and gives rise to two primary bile acids: cholate and Chenodeoxycholate. Newly synthesized bile acids are conjugated with glycine or taurine and secreted into the biliary tree; in humans, most of the bile acids are conjugated to glycine. Conjugation is a very important step in bile acid synthesis converting weak acids to strong acids, which are fully ionized at biliary and intestinal pH, making them hydrophobic (lipid soluble) and membrane impermeable. These properties aid in digestion of lipids and also decrease the passive diffusion of bile acids across cell membranes during their transit through the biliary tree and small intestine. This allows maximum lipid absorption throughout the small intestine without sacrificing bile acid loss.

**Enterohepatic Circulation**

After their involvement in micelle formation, about 95% of the conjugated bile salts are reabsorbed in the terminal ileum and returned to the liver via the portal venous system for eventual recirculation in a process known as enterohepatic circulation; only a small proportion (3-5%) are excreted into the feces. Enterohepatic circulation requires carrier-mediated transport by the terminal ileal enterocytes and the hepatocytes by means of both apical and basolateral transporters. First, the bile acids are actively transported from the intestinal lumen into the enterocyte via a network of efficient sodium-dependent apically located co-transporters (ileal bile acid transporters) in the distal ileum up to 100 cm proximal to the ileocecal valve. The bile acids are then transported into the portal venous system via a basolateral transport system consisting of 2 proteins, organic solute transporter (OST)-α and OST-β, and returned to the liver. In the liver, they are efficiently extracted by basolateral transporters on the hepatocytes and added to the bile acid pool. The liver must then only replace the small amount of bile acids that are not recirculated and instead excreted into the feces (about 0.3-0.5 g/day). In humans, approximately 12 g of bile acids are secreted into the intestine daily. Efficient recycling allows the maintenance of a bile acid pool of about 2-3 g which typically cycles 4-6 times/day.

The size of the bile acid pool is tightly controlled by a complex regulatory pathway. Bile acid synthesis is under negative feedback regulation by which bile acids downregulate their own biosynthesis by binding to the nuclear receptor, farnesoid X receptor (FXR), thereby inducing the synthesis of a repressor protein which downregulates the rate-limiting enzyme in bile acid synthesis, CYP7A1. Recently, fibroblast growth factor 19 (FGF19), acting via FXR, was shown to be stimulated by bile acids in the ileal enterocyte. FGF19 is then released from the enterocyte and travels to the liver where, acting together with β-klotho, it activates the FGF receptor 4 (FGFR4) on the hepatocyte leading to a phosphorylation cascade that downregulates bile acid synthesis (Figure 2).

As previously noted, a small proportion of the secreted bile acids reach the colon where they are deconjugated (removing the taurine or glycine) and dehydroxylated (removing the 7-OH group) by bacteria to produce the secondary bile acids, deoxycholate and lithocholate. A small fraction of these secondary bile acids are absorbed by the colonic epithelium; however, most are eliminated in the feces.

**Bile Acid Function**

Bile acids play a key role in the absorption of lipids in the small intestine. Upon stimulation by a meal (via cholecystokinin release), bile acids are expelled from the gallbladder into the bile duct and then enter the lumen of the small intestine where they solubilize dietary lipids in a multistep process. First, they...
emulsify the lipids, allowing the droplets to disperse and increasing the surface area for digestive enzymes. Next, they form micelles with the products of lipid digestion, allowing the normally hydrophobic lipids to dissolve into the aqueous luminal environment. The micelles then diffuse to the brush-border membrane of the intestinal epithelium whereby the lipids are released from the micelles and diffuse down their concentration gradients into the cells. Once released, the bile acids are left behind in the intestinal lumen until they are absorbed in the terminal ileum. Their presence in the intestinal lumen allows maximal absorption of lipids throughout the small intestine; however, the majority of fat absorption occurs in the proximal 100 cm of the jejunum.

Multiple other functions of bile acids have also been described, including:

- Contributing to cholesterol metabolism by promoting the excretion of cholesterol
- Denaturing dietary proteins, thereby accelerating their breakdown by pancreatic proteases
- Having direct and indirect antimicrobial effects
- Acting as signaling molecules outside of the gastrointestinal tract, thereby representing another mechanism by which the gut microbiota influences the metabolism of the host.

**Role of Bile Acids in Diarrheal Disorders**

Excess bile acids entering the colon contribute to the classical symptoms associated with BAM including watery diarrhea, bloating, fecal urgency and fecal incontinence by stimulating colonic secretion and motility. Bile acids stimulate secretion in the colon by activating intracellular secretory mechanisms, increasing mucosal permeability, inhibiting Cl⁻/OH⁻ exchange and enhancing mucus secretion. Colonic water secretion depends on the concentration of bile acids, with concentrations typically above 3 mmol/L leading to secretion. Bile acids stimulate motility by inducing propulsive contractions thereby shortening colon transit time, potentially worsening urgency and diarrhea. Interestingly, a recent study suggests that low concentrations of bile acids downregulate colon secretion and promote fluid and electrolyte absorption.

In contrast, when colonic luminal concentrations of bile acids are high, as is seen in BAM, bile acids induce prosecretory and promotility effects, manifesting clinically as diarrhea.

**Prevalence of Bile Acid Diarrhea**

Due to the limited availability of diagnostic tests for BAM, its prevalence remains unclear. The availability of the ⁷⁷Selenium-homocholic acid taurine (SeHCAT) retention test (see below) in Europe has, nevertheless, allowed an estimate of its prevalence, at least in the Western world. A systematic review of studies that estimated the prevalence of primary bile acid diarrhea using the SeHCAT test in patients with chronic unexplained diarrhea [most of whom were classified as diarrhea-predominant irritable bowel syndrome (D-IBS)] identified 18 studies involving 1223 patients. At the best confidence interval (<10%) for SeHCAT retention percentage, one-third of patients had an abnormal result suggesting BAM. Using this figure, these investigators have estimated the population prevalence of bile acid diarrhea based upon the population with D-IBS. For example, if it’s estimated that approximately 90 million people worldwide suffer from IBS, approximately one-third, or 30 million, have bile acid diarrhea. In the United Kingdom, the prevalence in the general population has been estimated to be over 1%. Therefore, although bile acid diarrhea is often considered rare, this appears not to be the case.

**Diagnosis of Bile Acid Diarrhea**

The diagnosis of BAM is difficult as measurement of fecal bile acids in a 24-hour stool collection, the definitive method, is unpleasant and is available only in a few research laboratories. Additionally, the SeHCAT test, a nuclear medicine test more appropriate for clinical practice that measures loss of bile acids in a simple and reliable manner, has never been approved for use in the United States and is not widely available in the rest of the world. This has clearly hindered the recognition of BAM in patients with chronic diarrhea. Another test of BAM that has fallen from favor and is more of historical interest is the ¹⁴C-glycocholate breath test. In the SeHCAT test, first described in 1981, the selenium-labeled bile acid is administered orally and the
Bile Acids

NUTRITION ISSUES IN GASTROENTEROLOGY, SERIES #110

total body retention is measured with a gamma camera after 7 days. A retention value of less than 10% is indicative of BAM and highly predictive of a successful therapeutic response to bile acid sequestrants. This test has a sensitivity for diagnosing BAM of 80-90% and a specificity of 70-100%, and offers a low radiation dose to the patient.

More recently, the measurement of 7-α-hydroxy-4-cholesten-3-one (C4) levels in the plasma has been proposed as an indicator of BAM. Plasma C4 levels increase when bile acid synthesis increases, and C4 levels are substantially elevated in BAM patients with a sensitivity and specificity of 90% and 77%, respectively for type 1 BAM (see below) and 97% and 74%, respectively for type 2 BAM (see below).

Furthermore, C4 levels have been shown to correlate well with SeHCAT retention. Despite its obvious advantages in the diagnosis of BAM, to our knowledge, at present, this test is available for research use only. Perhaps with the expanding availability of mass spectroscopy in diagnostic laboratories, this test will become more widely available.

Given the limited diagnostic testing for BAM currently available, particularly in the United States, a “therapeutic trial” with a bile acid sequestrant (see below) is often used as a diagnostic tool. If the treatment results in resolution or improvement of the diarrhea, the response is considered supportive evidence of BAM. This approach is supported by the pooled data from a report showing a dose-response relationship according to severity of malabsorption, as determined by SeHCAT retention, to treatment with a bile acid sequestrant. Although this approach has the advantage of not requiring specialized investigations, as treatment is often poorly tolerated and response variable, this strategy is difficult to strongly advocate without a definitive diagnosis.

Bile Acid Malabsorptive Disorders

Many conditions cause BAM and may be divided into three types depending upon their etiology (Table 1). Type 1 BAM results from terminal ileal resection/bypass or disease (e.g., Crohn’s disease) which results in failure of enterohepatic recycling of bile acids and excess amounts entering the colon. Type 2 BAM, often referred to as primary (or idiopathic) bile acid diarrhea, occurs in the setting of otherwise normal (grossly and histologically) gastrointestinal and hepatobiliary systems. Potential mechanisms contributing to this type of BAM are discussed below. Finally, type 3 BAM includes causes of BAM not included with types 1 and 2 that may interfere with normal bile acid cycling, small intestinal motility or composition of ileal contents. A selection of specific causes of BAM is discussed further below.

Short Bowel Syndrome

Terminal ileum resection affects the reabsorption of bile acids into the enterohepatic circulation. Resection of less than 100 cm of terminal ileum will interrupt the normal feedback, resulting in increased bile acid synthesis and an increased concentration of unabsorbed bile acids entering the colon. When more than 100 cm of distal ileum in adults is resected, the most common bowel anatomy in short bowel syndrome (SBS), the resulting reduction in bile acid absorption exceeds the liver’s ability to synthesize adequate replacement. This ultimately results in a decreased bile acid pool with impaired micelle formation and fat digestion, and manifests clinically as steatorrhea and fat soluble vitamin deficiencies. Maximum bile acid synthesis (5-10 mmol/day) is less than daily bile acid secretion in healthy patients (about 25-30 mmol/day).

Further aggravating bile acid function in SBS is the common occurrence of small intestinal bacterial overgrowth which results in the deconjugation of bile

(continued on page 38)
acids in the small bowel. Moreover, the absence of the ileum also contributes to the diarrhea because of both the loss of epithelial absorptive capacity and loss of the “ileal brake” resulting from diminished production of motility-inhibiting gut hormones (glucagon-like peptide 1 and peptide YY) that are produced in the L cells of the distal ileum and proximal colon. In SBS patients with residual colon, the synthetic conjugated bile acid, cholylsarcosine, was shown to increase fat absorption and body weight without aggravating diarrhea. Ox bile supplementation has also shown benefit in an uncontrolled case study. Unfortunately, these products are not commercially available. The use of bile acid sequestrants, such as cholestyramine, may worsen fat digestion and should generally be avoided in the SBS patient.

Diarrhea-predominant Irritable Bowel Syndrome

BAM has been documented in up to 50% of patients diagnosed with functional diarrhea and D-IBS. Ileal perfusion of bile acids has been shown to result in greater ileal fluid secretion in IBS patients compared to healthy volunteers. In a small, randomized, double-blind, placebo controlled trial of colesevelam hydrochloride, a bile acid sequestrant, in patients with D-IBS, colonic transit at 24 hours was delayed in the ascending colon by an average of 4 hours compared with placebo. It was also associated with greater ease of stool passage and somewhat firmer stool consistency. Recently, single nucleotide polymorphisms of FGFR4 and β-klotho were found that identified a subset of D-IBS patients who received a beneficial response to colesevelam.

Microscopic Colitis

Up to 43% of patients with microscopic colitis have evidence of BAM with a high response rate to treatment using a bile acid sequestrant suggesting a pathophysiological role of bile acids in this condition. In a study of 51 patients with either lymphocytic or collagenous colitis, 22 (43.1%) patients were found to have BAM. The frequency of BAM was higher in lymphocytic colitis than in collagenous colitis (60% vs 27%). Treatment with a bile acid sequestrant induced clinical remission in 19 of 22 patients with both microscopic colitis and BAM; no clinical remission was seen in patients without BAM. Therefore, BAM seems to be common in patients with microscopic colitis, particularly lymphocytic colitis, suggesting that idiopathic BAM and microscopic colitis are often concomitant conditions. In this setting, bile acid sequestrant use seems to be highly effective in stopping diarrhea.

Primary Bile Acid Diarrhea

Limitations of the data notwithstanding, as discussed earlier, it would appear that idiopathic or primary bile acid diarrhea (PBAD) is the most common cause of BAM and may account for at least 30% of individuals who would otherwise be labeled as having D-IBS or functional diarrhea. Importantly, the current definition of PBAD requires that there be a grossly and histologically normal ileum and good response to treatment with a bile acid sequestrant. Despite much investigation, until recently the pathogenesis of PBAD

Table 1. Causes of Bile Acid Malabsorption

<table>
<thead>
<tr>
<th>Etiology of BAM</th>
<th>Consider BAM if Symptomatic</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Type 1</strong></td>
<td>Terminal ileal resection or bypass</td>
</tr>
<tr>
<td></td>
<td>Terminal ileal disease (e.g., Crohn’s disease)</td>
</tr>
<tr>
<td><strong>Type 2</strong></td>
<td>No definitive etiology</td>
</tr>
<tr>
<td></td>
<td>No demonstrative ileal disease</td>
</tr>
<tr>
<td><strong>Type 3</strong></td>
<td>Small intestinal bacterial overgrowth</td>
</tr>
<tr>
<td></td>
<td>Post-cholecystectomy</td>
</tr>
<tr>
<td></td>
<td>Post-vagotomy</td>
</tr>
<tr>
<td></td>
<td>Celiac disease</td>
</tr>
<tr>
<td></td>
<td>Radiation enteritis</td>
</tr>
<tr>
<td></td>
<td>Chronic pancreatitis</td>
</tr>
</tbody>
</table>
has been poorly understood. A number of mechanisms have been proposed including mutations in ileal bile acid transporters and rapid small bowel transit causing diminished ileal epithelial contact time.48-53 Neither of these mechanisms, however, have strong supporting data nor have the findings not been consistently demonstrated.

Most recently, a role of altered feedback inhibition of bile acid synthesis has been proposed and its support is gaining momentum.54 This altered feedback regulation is thought to be mediated by FGF19 (fibroblast growth factor 19).55-57 Walters and colleagues recently found that patients with PBAD had a marked decrease in plasma levels of FGF19, about 50% that of controls, and this level correlated inversely with bile acid synthesis as measured by the serum level of the bile acid precursor 7-α-hydroxy-4-cholesten-3-one (aka “C4”, see Figure 1).58 As a consequence of this deficiency, the hepatocytes are unable to downregulate bile acid synthesis. It was speculated that this disrupted feedback

### Table 2. Commercially-available Bile Acid Sequestrants

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage</th>
<th>Side Effects</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cholestyramine</td>
<td>4-gram packet 1 to 6 times/day</td>
<td>Nausea, vomiting, flatulence, bloating, abdominal discomfort, constipation, fecal impaction, anorexia, steatorrhea, urticaria</td>
<td>- Poor taste may affect adherence</td>
</tr>
<tr>
<td>(Questran®, Questran® Light, Prevalite®, LoCHOLEST®, LoCHOLEST® Light)</td>
<td></td>
<td></td>
<td>- May interfere with the absorption of some medications (warfarin, diuretics, thyroid hormone, beta-blockers, digoxin) and fat-soluble vitamins; medications should be taken 1-hour before or &gt; 4-hours after bile acid sequestrant administration</td>
</tr>
<tr>
<td>Colestipol</td>
<td>5-gram packet 1 to 6 times/day</td>
<td>Same as above</td>
<td>- Same as above</td>
</tr>
<tr>
<td>(Colestid®)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Colesevelam</td>
<td>1.25 to 3.75 g/day</td>
<td>Constipation, dyspepsia, nausea, nasopharyngitis, headache, asthenia, influenza-type symptoms, rhinitis, hypoglycemia in diabetic patients, myalgias, hypertension</td>
<td>- Does not decrease the absorption of co-administered medications</td>
</tr>
<tr>
<td>(WelChol®)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
control by FGF19 may result in a large bile acid pool with incomplete ileal absorption and increased bile acid delivery to the colon causing diarrhea. The exact nature of the defect that leads to altered FGF19 production or release requires further investigation.

Treatment of Bile Acid Diarrhea

Treatment of patients with bile acid diarrhea secondary to another cause (e.g., active Crohn’s ileitis, microscopic colitis, small intestinal bacterial overgrowth) should target the underlying disease. Unfortunately, for most patients with bile acid diarrhea, no such cause is found or is effectively treatable. Therefore, for over 40 years, the treatment of bile acid diarrhea has relied on the use of oral administration of bile acid sequestrants.69 These agents are positively charged indigestible resins that bind the bile acids in the intestine to form an insoluble complex that is excreted in the stool preventing their secretomotor actions on the colon. There are currently three bile acid sequestrants commercially available, albeit for a non-United States Food and Drug Administration (FDA)-labeled indication (i.e., off label use): cholestyramine, colestipol, and colesevelam (Table 2).

Cholestyramine and colestipol are FDA-approved for the treatment of hypercholesterolemia (both agents) and pruritus related to partial biliary obstruction (cholestyramine only). Most patients with abnormal SeHCAT retention have been found to respond to treatment with cholestyramine: 96% response in patients with SeHCAT retention <5%, 80% response when <10% retention, and 70% response when <15% retention.24 However, as a powdered resin, their use has historically been limited by their unpleasant taste, which can lead to poor adherence with long-term use. Indeed, 40% to 70% of patients given bile acid sequestrants discontinue them.66,67 Furthermore, gastrointestinal side effects are common and include nausea, borborygmi, flatulence, bloating, and abdominal discomfort which can be present in as high as 30% of patients.62 Constipation may also occur, making titration of the dose important. For cholestyramine, the most commonly used bile acid sequestrant, starting with one 4 gram packet a day (5 grams for colestipol) and titrating upward as needed (maximum 6 times/day for both agents) seems to be an effective strategy. Colestipol also comes in tablet form; a form worth considering if the powder form is poorly tolerated. Other tips for improving the palatability of bile acid sequestrants are mentioned in Table 3.

Colesevelam is a newer bile acid sequestrant that binds bile acids with a higher affinity than either cholestyramine or colestipol. Importantly, a tablet form is available, improving its patient acceptability.63 Colesevelam is FDA-approved to treat hypercholesterolemia and, interestingly, as an adjunct treatment for type 2 diabetes mellitus. In a retrospective chart review and patient questionnaire, colesevelam at doses between 1.25 and 3.75 g/day was found to be well tolerated and effective in patients with BAM after cancer treatment, including some who had failed prior cholestyramine therapy.64 As previously mentioned, colesevelam was found to be more effective than placebo in a small, randomized controlled trial in patients with D-IBS with regards to symptom control and colon transit.65 Furthermore, single nucleotide

### Table 3. Tips to Making Bile Acid Sequestrants More Palatable

<table>
<thead>
<tr>
<th>Tip</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Add powder to a half cup of applesauce or other fruit sauce, strained baby fruits or crushed pineapple and mix thoroughly</td>
</tr>
<tr>
<td>2.</td>
<td>Add powder to a half cup of fruit drink, juice, or other non-caffeinated drink and mix thoroughly</td>
</tr>
<tr>
<td>3.</td>
<td>Add powder to a half cup of milk or broth</td>
</tr>
<tr>
<td>4.</td>
<td>Refrigerate the mixture</td>
</tr>
<tr>
<td>5.</td>
<td>Stir well</td>
</tr>
<tr>
<td>6.</td>
<td>Mix it with half water to dissolve it first, then finish it off with a thick type juice/nectar or smoothie</td>
</tr>
<tr>
<td>7.</td>
<td>Try mixing with pudding or custard</td>
</tr>
</tbody>
</table>

(continued on page 42)
polymerisms of FGFR4 and β-klotho have been found that appear to identify a subset of D-IBS patients who may benefit from colestervam.

Importantly, cholestyramine and colestipol interfere with the absorption of some medications (e.g., warfarin, diuretics, thyroid hormone, beta-blockers, digoxin) and fat-soluble vitamins. Therefore, these other medications should be taken 1-hour before or at least 4-hours after bile acid sequestrant administration. Apparently, colesvelam does not decrease the absorption of co-administered medications, presumably because of differences in chemical structure compared to cholestyramine and colestipol. Because bile acid sequestrants are not absorbed, they have no systemic side effects.

**CONCLUSION**

BAM appears to be a common cause of watery diarrhea; however, its role seems to be poorly appreciated among clinicians. As a consequence, bile acid diarrhea remains an underrecognized cause of chronic diarrhea and results in many patients receiving an incorrect diagnosis, thereby delaying proper treatment. Given the limitations in the availability of diagnostic testing and difficulties in completing an adequate empiric trial of a bile acid sequestrant, bile acid diarrhea is likely to remain a problematic diagnosis, at least for the near future. The development and validation of a relatively simple and inexpensive laboratory-based diagnostic test, such as the plasma measurement of C4, will hopefully change this scenario. Although the current treatment of BAM remains the use of bile acid sequestrants, the availability of colesvelam has improved patient tolerability to this form of therapy. Perhaps a more specific therapy, such as a FGF19 or FXR agonist, will become available for clinical use in the future.

**References**


(continued from page 40)

... polymorphisms of FGFR4 and β-klotho have been found that appear to identify a subset of D-IBS patients who may benefit from colesvelam.

Importantly, cholestyramine and colestipol interfere with the absorption of some medications (e.g., warfarin, diuretics, thyroid hormone, beta-blockers, digoxin) and fat-soluble vitamins. Therefore, these other medications should be taken 1-hour before or at least 4-hours after bile acid sequestrant administration. Apparently, colesvelam does not decrease the absorption of co-administered medications, presumably because of differences in chemical structure compared to cholestyramine and colestipol. Because bile acid sequestrants are not absorbed, they have no systemic side effects.

**CONCLUSION**

BAM appears to be a common cause of watery diarrhea; however, its role seems to be poorly appreciated among clinicians. As a consequence, bile acid diarrhea remains an underrecognized cause of chronic diarrhea and results in many patients receiving an incorrect diagnosis, thereby delaying proper treatment. Given the limitations in the availability of diagnostic testing and difficulties in completing an adequate empiric trial of a bile acid sequestrant, bile acid diarrhea is likely to remain a problematic diagnosis, at least for the near future. The development and validation of a relatively simple and inexpensive laboratory-based diagnostic test, such as the plasma measurement of C4, will hopefully change this scenario. Although the current treatment of BAM remains the use of bile acid sequestrants, the availability of colesvelam has improved patient tolerability to this form of therapy. Perhaps a more specific therapy, such as a FGF19 or FXR agonist, will become available for clinical use in the future.

**References**


(continued from page 44)
Bile Acids

NUTRITION ISSUES IN GASTROENTEROLOGY, SERIES #110

(continued from page 42)


Hepatotoxicity Associated with the Use of White Flood, a Nutritional Supplement

by Stanley Martin Cohen, Elizabeth Heywood, Anjana Pillai, Joseph Ahn

Complementary and alternative medical (CAM) therapies are used by a large percentage of the US population. These agents are poorly regulated. Several of these agents have been associated with hepatotoxicity. We present the first case report of cholestatic hepatitis attributed to the use of White Flood, an herbal muscle-building supplement. A patient using this agent presented with significant cholestatic hepatitis. A full serologic and imaging evaluation failed to reveal any other likely sources. His liver tests normalized with removal of the suspected offending agent. Evidence to support White Flood as the causative agent include a correct temporal relationship, lack of other likely etiology after extensive evaluation, and resolution of symptoms after withdrawal of this agent. Clinicians should be aware that this supplement may have the potential to induce cholestatic hepatitis.

INTRODUCTION

Complementary and alternative medical (CAM) therapies include a variety of herbal and dietary supplements. The use of CAM therapy has been reported by a large percentage of the US population in a variety of survey studies.1-6 The use of herbal and dietary supplements has increased by 50% between 1997-2002.2 These agents are poorly regulated by drug administrations worldwide.

The US Congress defined the term “dietary supplement” in the Dietary Supplement Health and Education Act of 1994.7 Under this act, such supplements are categorized as food, rather than drugs. As such, the FDA must show that a supplement is unsafe before action may be taken. This is in contrast to drugs and medications which must be proven safe and effective before they are eligible for marketing.

The exact incidence of herbal-induced hepatotoxicity is unknown. Many patients do not report the use of these agents to their health-care providers. The United States Drug-Induced Liver Injury Network (DILIN) found that approximately 10% of drug-induced liver injury (DILI) could be attributed to the use of herbal and dietary supplements.8

Several herbal products have been implicated as causes of DILI. Recently, there have been reports of hepatotoxicity resulting from the use of herbal products for weight loss and muscle building, including Hydroxycut and Herbalife.9-16 These cases prompted the FDA in May of 2009 to release a warning recommending that consumers stop using Hydroxycut-containing products.17

White Flood™ (Controlled Labs, New Rochelle, New York) is an herbal muscle-building supplement which is touted as a pre-workout nitric oxide energy-enhancing drink.18 The product contains a variety of ingredients including calcium silicate, potassium gluconate, folic acid, selenium, citrulline, ornithine, carnitine tartrate, Carino-Syn ® beta-alanine, L-tyrosine, beet root, gamma-aminobutyric acid (GABA), glucuronolactone, caffeine, cocoa bean, Evodia rutaecarpa (a Chinese herbal agent), L-norvaline, sugar cane, vinpocetine (from the Vinca plant), zeaxanthin,
cryptoxanthin, lutein, Huperzia Serrata (used in Chinese herbal medications), malic acid, natural and artificial watermelon flavor, acesulfame potassium, and sucralose.

No previous reports of hepatotoxicity have been reported with the use of White Flood or its component ingredients. We report the first case of cholestatic hepatitis attributed to this muscle-building supplement.

Case Report

A 23 year old Caucasian male was referred to our liver center for evaluation of elevated bilirubin and jaundice. In February 2011, he began taking White Flood as an oral muscle building supplement when he began a weight-lifting program. He denied using any injection supplements or anabolic steroids. Between February 2011 and April 2011, he was able to gain approximately 20 pounds with significant increase in his muscle size, strength, and tone. In early May 2011, he began to notice dark urine, dysgeusia and anorexia. He stopped using the White Flood at that point. Within approximately one week, he noticed the onset of jaundice and pruritus. He had minimal relief with Benadryl and sought medical attention. He was placed on cholestyramine for symptomatic relief by his primary care physician, but due to progressively increasing bilirubin levels, he was referred to our institution.

The patient denied any prior history of hepatitis, liver disease or jaundice. There was no known family history of liver disease. The patient denied any GI bleeding, or confusion. Except for the White Flood, he had taken no other supplements, herbal agents, prescription medications, or illicit drugs prior to the onset of his symptoms. He denied any travel, toxic exposures, or ill contacts. Social history revealed no tobacco, alcohol, IV drug use, tattoos, or transfusions. Except for the jaundice and pruritus, his review of systems was unremarkable. Physical examination revealed grossly icteric sclera, but was otherwise normal. There was no hepatosplenomegaly, stigmata of chronic liver disease or asterixis.

Upon presentation, his CBC, electrolytes, INR and TSH were normal. His other pertinent chemistry trends are outlined in Table 1. Serologic evaluation was performed and revealed anti-nuclear antibody (ANA) negative, smooth muscle antibody (SMA) at 1:20, ceruloplasmin 47.9, anti-mitochondrial antibody (AMA) negative, hepatitis A IgM negative, hepatitis B surface antigen negative, hepatitis B core IgM negative, hepatitis C antibody negative and hepatitis C RNA negative.

An ultrasound revealed a normal examination except for a contracted gallbladder. The clinical impression was that the patient had developed an acute supplement-induced hepatitis due to the White Flood. Despite his rising bilirubin, he showed no evidence of impending liver failure. The decision was made to avoid liver biopsy, continue symptomatic treatment with the cholestyramine and follow serial labs. The patient was instructed to avoid the use of any medication or supplements except as prescribed by us.

Within 2 weeks of seeing us, he began to feel better (continued on page 48)

Discussion

The use of complementary and alternative medical and herbal dietary supplements has been growing in popularity over the last several years. This is likely due to the cost and adverse effects of prescription medications, as well as a perception that herbal remedies are safer and have no adverse effects. In fact, many case reports and case series are available demonstrating hepatotoxicity from a wide variety of herbal supplements. We present another case report of such an adverse event associated with the use of a new energy enhancing supplement used to promote muscle growth.

White Flood is marketed as an energy-enhancing drink which is touted to enhance the natural effects of weight lifting. The product contains a variety of ingredients including vitamins, minerals, and herbs.

To our knowledge, this is the first reported case of hepatotoxicity associated with the use of White Flood. Review of the published literature did not reveal any previous case reports of hepatotoxicity from this agent. In addition, none of the individual ingredients have previously been specifically implicated as causes of hepatotoxicity.

The exact mechanism of hepatotoxicity from this supplement is unclear. However, as noted above, there are multiple ingredients in this agent. It is possible that one of the ingredients or several of the ingredients interacting together could have contributed to the hepatotoxicity.

As with any case report of a suspected liver injury from a supplement, there can be no unequivocal, definitive guarantee that White Flood was the causative agent. However, given the lack of prior liver disease, no other potential medications or supplements, a reasonable temporal relationship of liver damage after the ingestion, negative viral, autoimmune, and metabolic serologies, and the resolution of symptoms after removal of the suspected offending agent, the etiology of his cholestatic hepatitis seems extremely likely to be the White Flood. Given a lack of evidence supporting that the patient was developing frank liver failure (i.e. normal INR and mental status), the decision was made to avoid a liver biopsy. Because there is no pathognomonic liver biopsy of drug-induced hepatotoxicity, the biopsy would only have provided supporting evidence of DILI rather than an absolute diagnosis anyway. Although it would be the gold standard to prove causation, a rechallenge with White Flood would not be ethical or safe.

Clinicians should be made aware of the possibility that White Flood, a supplement used to promote muscle and weight increase, may have the potential to induce cholestatic hepatitis. An increased effort to educate clinicians and patients about the potential risk of herbal-associated hepatotoxicity is warranted. Clinicians should continue to question patients with unexplained hepatitis or jaundice about the use of medications as well as herbal supplements.

References

17. Available at URL:http://www.fda.gov/ForConsumers/ConsumerUpdates/ucm152152.htm
18. Available at URL:http://www.whiteflood.com
Does Parenteral Nutrition Cycling Reduce Cholestasis in Pre-term Infants?

It is known that prolonged parenteral nutrition (PN) use causes parenteral nutrition-associated cholestasis (PNAC) in premature infants. Prior studies have evaluated the effectiveness of cycling PN in children to see if the incidence of PNAC can be reduced. However, there are no studies evaluating the effect of cycling PN for preterm infants.

This prospective, randomized, controlled trial occurred in a neonatal ICU in which infants less than 1250 grams were enrolled and randomized in the first 5 days of life. Infants were randomized to receive either cycled PN (amino acid solution over 20 hours, intralipids over 18 hours, and dextrose over 24 hours) or continuous PN. Cholestasis from PNAC was defined as a direct bilirubin level greater than 2 mg/dL.

A total of 70 patients (34 receiving cycled PN and 36 receiving continuous PN) completed the study. Gestational age, birth weight, Apgar scoring, CRIB II (Clinical Risk Index for Babies II) scoring, incidence of antenatal steroid use, and incidence of chorioamnionitis were not different between the two groups. Duration of PN, number of nil per os (NPO) days, and number of days before starting trophic feeds were similar in both groups. However, the incidence of PNAC was similar in both groups (32% of cycled PN infants and 31% of continuous PN infants) with cholestasis typically occurring after the second postnatal week mark in both groups. Infants with and without PNAC subsequently were compared, and infants with a significantly lower gestational age, birth weight, Apgar scores, as well as higher CRIB II scores were more likely to develop PNAC. The presence of broncopulmonary dysplasia, total number of days on parenteral nutrition, and total days with NPO status were significantly greater in the PNAC group. The PNAC group also had a significantly greater number of days before trophic feeds were started and a greater total number of days before achieving full enteral feeds.

This study suggests that cycled PN does not reduce PNAC in preterm infants, and other clinical factors, such as a lower gestational age and delay before enteral feeds are initiated are associated with PNAC although further characterization of risk factors for PNAC remain to be determined.


John Pohl, M.D., Book Editor, is on the Editorial Board of Practical Gastroenterology
The new HUMIRA® (adalimumab) Talking Training Pen provides an important bridge from the doctor’s office to the patient’s home and a new advancement for patient education.

About the HUMIRA Talking Pen
The healthcare industry has only just begun to scratch the surface of the potential for adapting current consumer technologies to improve the patient experience. We have cars and even homes that talk to us, and technologies such as these are beginning to surface in healthcare. Abbott is taking the lead in patient experience, introducing the audio-enhanced HUMIRA® (adalimumab) Talking Training Pen, which trains patients on administering the medication. The Pen uses a multi-sensory approach, engaging sight, touch and hearing, to more effectively educate patients about HUMIRA.

The HUMIRA Talking Training Pen is designed to train patients experientially by engaging multiple senses (hearing, sight, touch) with the goal of helping patients use the HUMIRA Talking Training Pen properly and confidently. It also provides an in-office tool for healthcare professionals teaching patients about their medication.

The HUMIRA Talking Training pen is part of a new product training kit which provides simple, easy-to-understand information about HUMIRA and how to administer it. The pen serves as a training device that does not include a needle or medication, that allows patients to practice without administering the medication before they are ready. Patients simply press play to start the device and begin hearing the instructions in either English or Spanish.

The HUMIRA Talking Training Pen offers an educational bridge between the training the patient receives in the doctor’s office and the experience of administering their medication at home, helping to increase a patient’s confidence and provide supplemental support. For more information, visit our website: http://www.humira.com/myhumira/injection-training-kit.aspx
Or contact: Phyliss Milligan (847) 937-6477 Phyliss.milligan@abbott.com

GIQuIC Colonoscopy Quality Registry Surpasses 100,000 Cases
Milestone Underscores Value of Clinical Benchmarking Tool for Gastroenterology Practices

BETHESDA, MD. The GI Quality Improvement Consortium, Ltd. (GIQuIC), a joint initiative of the American College of Gastroenterology and the American Society for Gastrointestinal Endoscopy, announced today that more than 100,000 colonoscopy cases have been submitted to a national registry of endoscopic procedures.

GIQuIC registry participants have contributed real-time procedure related data from over 100,000 colonoscopies, not claims data, and the growth rate for the registry has increased to almost 2,000 new cases per week in recent months, with an accompanying surge in the growth of the number of practices involved in this quality improvement effort.

GIQuIC is a national registry that fosters the ability of endoscopists and endoscopy facilities to benchmark themselves, and provides impetus for quality improvement. Some 84 data fields for colonoscopy are collected and ten quality measures are benchmarked, including rate of cecal intubation, adenoma detection rate, prep assessment, and appropriate indications for procedure, among others. Currently, hundreds of physicians from endoscopy centers nationwide have registered to participate in this ground-breaking initiative.

The collection of real-time data from more than 100,000 colonoscopies is an important milestone for those gastroenterologists who were early adopters of GIQuIC and whose forward thinking helped reach this threshold. “Every additional user makes the registry more valuable for everyone else who uses it,” commented Irving Pike, M.D., FACP, FASGE, President of the GIQuIC Board. “As the data accumulates, the potential value of GIQuIC, not only as a national benchmarking
tool, but also as a research database, grows,” he added.
“Reaching 100,000 cases in such a short time has exceeded our expectations. We expect this number will steadily increase as there is more emphasis from payers and the Centers for Medicare & Medicaid Services for physicians to document compliance with quality measures,” said Glenn M. Eisen, MD, MPH, FASGE, Director and Secretary of the GIQuIC Board. “Right now, participation in quality improvement programs is voluntary, but it will be required by law in the next two years. GIQuIC is leading the way among reporting systems and helping physicians meet quality compliance requirements.”

“GIQuIC has made it simple and easy to track our procedural volume and quality. This has allowed the physicians to monitor their performance to ensure it is meeting quality standards,” commented Michael S. Morelli, MD, CPE, FACG, a GIQuIC user. “Prior to GIQuIC, the doctors had no idea how well they were performing colonoscopy procedures. GIQuIC has changed that,” he added.

The ease of use and the value of the data generated by GIQuIC, both for benchmarking with accreditation agencies as well as demonstrating quality performance to insurance providers, has been a key benefit for registry participants. According to Laura Allen, RN and clinical director of an endoscopy center, “GIQuIC is a handy reference for the physicians in our practice to readily review their performance and how they compare to others in the practice, as well as to benchmark against national statistics. This is a wonderful way for the physicians to demonstrate to the community and to themselves that they are doing an outstanding job and performing procedures in a quality manner.”

The economic benefits of the GIQuIC registry include the value to endoscopy centers of the data on quality performance to secure better reimbursement contacts and to be recognized as a group of highly preferred providers, according to Ms. Allen.

Additionally, recent feedback from other GIQuIC participants suggest savings to GI practices by using the GIQuIC registry as a mechanism to collect data that would otherwise use staff time. In one case, a 6-person GI practice in Virginia reported savings equivalent to the cost of a full-time employee by using the GIQuIC registry as a mechanism to collect data that would otherwise use staff time.

**About GIQuIC**

The GI Quality Improvement Consortium, Ltd. (“GIQuIC”) is an educational and scientific 501(c) (3) organization established by gastroenterologists, physicians specializing in digestive disorders. GIQuIC is a joint initiative of the American College of Gastroenterology (ACG) and the American Society for Gastrointestinal Endoscopy (ASGE). Gastroenterologists treat patients for disorders and conditions of the digestive tract. GIQuIC has developed and utilizes various measurements of the endoscopic techniques of practicing gastroenterologists, a process referred to as benchmarking. This national benchmarking project began by measuring common endoscopic procedures employed by gastroenterologists. Endoscopy is a minimally invasive medical procedure that is used to assess the digestive system organs by inserting a tube orally into a patient’s stomach or rectally into the patient’s colon. The physician founders of the GIQuIC believe that the scientific measurement of the quality of endoscopic procedures will improve the quality of the medical care being given to patients throughout the United States and abroad, and ultimately will improve the quality of public health. For more information about the GIQuIC registry, visit www.giquic.org

(continued on page 54)
(continued from page 52)

About the American College of Gastroenterology
Founded in 1932, the American College of Gastroenterology (ACG) is an organization with an international membership of more than 12,000 individuals from 80 countries. The College is committed to serving the clinically oriented digestive disease specialist through its emphasis on scholarly practice, teaching and research. The mission of the College is to serve the evolving needs of physicians in the delivery of high quality, scientifically sound, humanistic, ethical, and cost-effective health care to gastroenterology patients. For more information, visit www.gi.org

About the American Society for Gastrointestinal Endoscopy
Since its founding in 1941, the American Society for Gastrointestinal Endoscopy (ASGE) has been dedicated to advancing patient care and digestive health by promoting excellence and innovation in gastrointestinal endoscopy. ASGE, with more than 12,000 members worldwide, promotes the highest standards for endoscopic training and practice, fosters endoscopic research, recognizes distinguished contributions to endoscopy, and is the foremost resource for endoscopic education. For more information, visit www.asge.org and www.screen4coloncancer.org

<table>
<thead>
<tr>
<th>Statement of Ownership Management and Circulation (Required by 39 U.S.C. 3685)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Title of Publication: PRACTICAL GASTROENTEROLOGY</td>
</tr>
<tr>
<td>Publication Number: 0277-4208</td>
</tr>
<tr>
<td>Filing Date: 10/1/12</td>
</tr>
<tr>
<td>Frequency: Monthly</td>
</tr>
<tr>
<td>Number of Issues Published Annually: 12</td>
</tr>
<tr>
<td>Annual Subscription Price: $145</td>
</tr>
<tr>
<td>Mailing Address and Business Headquarters:</td>
</tr>
<tr>
<td>Practical Gastroenterology Publishing, Inc., 99B Main Street, Westhampton Beach, NY 11978</td>
</tr>
<tr>
<td>Publisher: Vivian Mahl</td>
</tr>
<tr>
<td>Managing Editor: Adrien Mahl</td>
</tr>
<tr>
<td>Owner: Vivian Mahl</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Average # copies for 12-month period</th>
<th>Actual # copies for October 2012 issue</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total # copies (Net Press Run)</td>
<td>17,900</td>
</tr>
<tr>
<td>Paid and/or Requested Circulation through:</td>
<td></td>
</tr>
<tr>
<td>Dealers</td>
<td>—</td>
</tr>
<tr>
<td>Mail subscriptions</td>
<td>9,513</td>
</tr>
<tr>
<td>Total Paid and/or Requested</td>
<td>9,513</td>
</tr>
<tr>
<td>Free Distribution by Mail</td>
<td>8,327</td>
</tr>
<tr>
<td>Free Distribution Outside of Mail</td>
<td>—</td>
</tr>
<tr>
<td>Total Free Distribution</td>
<td>8,327</td>
</tr>
<tr>
<td>Total Distribution</td>
<td>17,900</td>
</tr>
<tr>
<td>Copies Not Distributed</td>
<td>100</td>
</tr>
<tr>
<td>Return from New Agents</td>
<td>—</td>
</tr>
<tr>
<td>TOTAL</td>
<td>17,940</td>
</tr>
<tr>
<td>Percent Paid and/or Requested Circulation</td>
<td>53%</td>
</tr>
</tbody>
</table>

I certify these statements are correct and complete
Vivian Mahl, Publisher
PS Form 3526
For additional information about products and services that appear in Practical Gastroenterology, check the appropriate boxes on this coupon, fill in your name and address and send it to:

Practical Gastroenterology
99B Main Street, Westhampton Beach, NY 11978
Or send your form via fax to: (631) 288-4435

Although every effort has been made to ensure the accuracy of this index, we cannot absolutely guarantee against the eventuality of last minute changes or omissions.

Beutlich LP, Pharmaceuticals
- HurriCaine ONE ................................................. 41
- Bracco ............................................................. 43
- Braintree Laboratories, Inc.
  - SuPrep .......................................................... Covers 4, 3
- CCA Alliance .................................................... 55
- Ferndale Healthcare, Inc. ..................................... 47
- Ferring Pharmaceuticals
  - Prepopik ....................................................... 8-10
- Forest Laboratories, Inc.
  - Linzess ......................................................... 17, 18
- Given Imaging .................................................. 13
- Hepatitis Foundation ........................................... 53
- HMB Endoscopy Products ................................... 57
- Imedex ............................................................ 49
- Konsyl Pharmaceuticals, Inc.
  - Sitzmarks ...................................................... 33
- Otsuka
  - BreathTek ..................................................... 5, 6
- Quintron
  - Breath Testing ................................................ 37
- Salix Pharmaceuticals
  - Solesta .......................................................... Cover 2; 1, 2
- Shire US, Inc.
  - Lialda ............................................................ Cover 22-25
- Sigma-Tau Pharmaceuticals, Inc.
  - VSL#3 & VSL#3 DS ......................................... 29

Although every effort has been made to ensure the accuracy of this index, we cannot absolutely guarantee against the eventuality of last minute changes or omissions.

Name
Hospital/Company
Address
Suite/Apt #
City
State
Zip
Phone
Area Code

Please place one letter or numeral in each box provided.
MEETINGS CALENDAR

December 13-15, 2012
2012 Advances in Inflammatory Bowel Diseases, Crohn’s & Colitis Foundation’s Clinical & Research Conference
The Westin Diplomat, 3555 South Ocean Drive, Hollywood, FL. The premier IBD meeting of the year. Two workshops, The Future of IBD and The Basics of IBD, will be held at the conference. This “can’t miss” event will inform healthcare professionals and researchers of advances and breakthroughs in the field in an effort to stimulate better care and research for patients. The outstanding faculty is comprised of expert specialists who will lead the sessions and interact with the conference attendees. For more information visit: http://www.advancesinibd.com/2012/index.asp

May 18–21, 2013
Digestive Disease Week
Orange County Convention Center, Orlando, FL. Digestive Disease Week® (DDW) is the largest and most prestigious meeting in the world for the GI professional. Every year it attracts approximately 15,000 physicians, researchers and academics from around the world. DDW is jointly sponsored by four societies:
• The American Association for the Study of Liver Diseases (AASLD)
• The American Gastroenterological Association (AGA)
• The American Society for Gastrointestinal Endoscopy (ASGE)
• The Society for Surgery of the Alimentary Tract (SSAT)
Learn about new developments in your field. Review the latest and best basic, translational, and clinical research in gastroenterology, liver disease, endoscopy and gastrointestinal surgery. Attend high-quality educational programs. Choose from over 400 sessions, including clinical and research symposia, state-of-the-art lectures and research and topic fora, covering a wide array of topics and presented by a world-renowned faculty unsurpassed in their field. Network with colleagues. Partake in an array of networking and social opportunities to meet fellow digestive disease specialists from around the globe. Try new products. DDW’s exhibit hall hosts hundreds of companies showcasing the latest GI products and services. For more information visit: http://www.ddw.org
ACROSS

1 Third TNF inhibitor to be approved in the U.S.
6 ___ acid
10 Cause to occur
11 They are used in trials
12 Ulnar site
14 It’s on patient questionnaires
16 Dia____
18 Supplement
20 The state held in common by a series of genes
22 Active cause
24 Extramedullary hematopoiesis, for short
25 Cerium symbol
26 Providing support
29 Diethyinitrosamine, for short
30 Immune system components
32 The S in SDS
35 __mentary
36 To the same degree
37 Specialist in operations
38 John Lawrence was known as the father of this form of medicine

DOWN

1 Relating to one of the sacs in a compound gland
2 Band-___
3 Receives
4 Type of light, abbr.
5 Angioimmunoblastic lymphoma, for short
7 An organelle in the cytoplasm of a living cell
8 Abnormal developments
9 Form of diagnostic test used in nuclear medicine
13 Created
15 Inventor of a thermometer
17 Not dangerous to health
18 Patient’s form entry
19 Long linear polymer found in the nucleus of a cell and formed from nucleotides
21 ____’s sign: severe pain in the epigastric region, a premonitory symptom of eclampsia
22 pH imbalance in the body
23 Nodule
27 Cure, in a way
28 The K in JNK
31 “This ___ test” (2 words)
33 Myeloproliferative neoplasm, for short
34 ___ invasive surgery
36 Light metal symbol

(Answers on page 52)